93. (Amended) The method of eliciting protective antibodies specific to group A streptococcal polysaccharide according to claim 81, wherein the conjugates are administered in a dosage amount of about 0.1 μg to about 10 μg per kilogram of body weight.

REMARKS

Claims 80-93 are pending in this application and stand rejected.

The preamble of claim 80 has been amended by adding the recitation: "eliciting protective antibodies specific to group A streptococcal polysaccharide in a mammal". The support for this amendment is found throughout the specification, for example, at the last paragraph of page 17 through the first paragraph of page 18 of the application as originally filed states: "The immunogenic compositions of the invention may be used as a means for raising antibodies useful for prophylactic and diagnostic purposes...As used herein, the vaccines of this invention are capable of eliciting antibodies useful for providing protection against infection of group A streptococcal bacteria." Also, support for claiming "antibodies specific to group A streptococcal polysaccharide" is found, for example, at page 10, lines18-22: "The resulting data demonstrate that these antibodies are opsonic and the epitope to which these opsonic group A carbohydrate antibodies are directed are the non-reducing terminal N-acetylglucosamine residues."

Claims 81 and 83-93 have been amended to maintain proper antecedent basis with claim 80. Support for the addition of the term "conjugate" to claim 93 is found at page 18, line 33 to page 19, line 1, of the application as originally filed. No new matter is introduced by the Amendment. Entry of the Amendment is respectfully requested.

Response to Rejection under 35 U.S.C. §112, Second Paragraph

Claims 80-93 were rejected under 35 U.S.C. §112, Second Paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the instant application.

Claim 80 was rejected as being indefinite for the recitation "conjugate of formula (I)". Applicants have amended the claim to recite "polysaccharide component of said conjugates is of formula (I)". The Examiner also rejected claim 80 for lacking proper antecedent basis for

the recitation "linked to protein or protein fragment". Applicants have amended claim 80 by reciting "bound to the protein component or protein fragment component of said conjugates". Claim 80 was also rejected because the Examiner found confusion as to whether there was a distinction of meaning between the recitations "protective response in the mammal" in the last line of the claim, and the recitation "protective immune response in a mammal" in line 1 of the claim. Applicants have amended claim 80 so that neither recitation appears in claim 80. Finally, claim 80 was rejected as being indefinite for lacking proper antecedent basis for the recitation "the polysaccharide". Claim 80 has been amended to address the Examiner's concern by amending the rejected recitation to state "said polysaccharide component".

Claim 90 was rejected as being indefinite for lacking antecedent basis for the recitation "the polysaccharide is administered with an adjuvant". Claim 90 has been amended to recite "the conjugates are administered with an adjuvant".

Claim 93 was rejected as being indefinite for lacking proper antecedent basis for the recitation "the group A polysaccharide". Claim 93 has been amended to recite "group A streptococcal polysaccharide". Claim 93 was further rejected as being indefinite for the recitation "wherein the group A polysaccharide is administered in a dosage...". Claim 93 has been amended to recite "wherein the conjugates are administered in a dosage...".

Claims 81-93 were also rejected as being indefinite due to the rejection of indefiniteness of the base claim, claim 80. Claim 80 and dependent claims 81-93 have been amended to address the Examiner's concerns.

Applicants respectfully request reconsideration and removal of these grounds of rejection.

Response to Enablement Rejection under 35 U.S.C. §112, First Paragraph

Claims 80-93 were rejected under 35 U.S.C. §112, First Paragraph, because the Examiner contends that the specification does not provide enablement for a method of eliciting a protective immune response in a mammal against infection by group A streptococcal (GAS) bacteria comprising administering the polysaccharide of formula I conjugated either to a protein or a fragment of a protein, wherein n is about 1 to about 50 or about 3 to about 30. Although applicants have amended the claims, applicants respectfully disagree.

Specifically, the Examiner contends that undue experimentation is required to practice the invention due to the lack of disclosure as to: (1) the precise size of the polysaccharide of formula I that confers an average molecular weight to the polysaccharide that is large enough to be protective, and (2) the demonstration that one or more GAS polysaccharide (GASP) conjugates comprising the polysaccharide of formula I falling in the recited size range does elicit a protective immune response in a mammal, human or child against infection by GAS bacteria. Applicants respectfully disagree for the following reasons recited below.

Applicants respectfully disagree with the Examiner's contention that the instant application does not enable the precise size of the polysaccharide of formula I that confers an average molecular weight to the polysaccharide that is large enough to be protective. At page 11, lines 5-19 of the instant application as originally filed, the specification discloses the size range of the GASP vaccine polysaccharide component to elicit a protective response in individuals (i.e., mammals): "...and n is a number of repeat units sufficiently large to define a polysaccharide of sufficient average molecular weight to be immunogenic. Preferably n is from about 1 to about 50. Even more preferably, n is from about 3 to about 30 with an optimal amount of about 20...Most preferably the average molecular weight is about 10 kilodaltons. A single repeat amount of the GASP has a molecular weight of about 500 daltons." In Example 7 of the instant application, the specification discloses that a GASP conjugate vaccine (where its polysaccharide component has an average molecular weight of 10 kilodaltons, see Example 6) was able to elicit the production of antibodies specific to GASP. This experiment, in the context of the entire specification, teaches that antibodies specific to GASP are protective against GAS infection (see below).

Example 1 of the instant application teaches that antibodies specific to GAS polysaccharides of formula I are protective against GAS bacteria. Example 1 first determined that sera samples from GAS infected individuals contained antibodies specific to GAS polysaccharides: "Having established that human sera do contain group A carbohydrate antibodies and that the titers of these antibodies do vary in individuals, we next addressed the question of whether these antibodies would also promote opsonophagocytosis in an *in vitro* assay system." (page 24, lines 1-5, of the application as originally filed).

The determination of whether antibodies specific to GAS polysaccharides are protective was shown in Example 1 of the instant application through a series of four

experiments: bactericidal assays, relationship between anti-CHO titers and opsonophagocytosis by human sera, studies of phagocytosis by human sera in heparinized blood versus heparin free assays and absorption experiments. The bactericidal assays established that human sera samples containing antibodies specific to GAS polysaccharide are protective, as these human sera severely abolished growth of GAS bacteria. As further evidence that human sera containing antibodies specific to GAS polysaccharide are protective, the opsonophagocytosis assays established a relationship between protection against GAS bacteria and antibodies specific to GAS polysaccharide: "As seen in Figure 6, all sera exhibiting titers (of antibodies against GAS carbohydrate, i.e. GASP) greater than 200,000 exhibited greater than 80% killing, while three out of the four sera with titers less than 200,000 did not." (page 25, lines 1-4, of the instant application as originally filed, parenthetical note added). The phagocytosis experiment with human sera in both heparin and heparin-free conditions provided further data on the protective ability of human sera which contain antibodies against GAS polysaccharides.

Finally, the absorption experiments provided the conclusive evidence that the antibodies specific to GASP in the human sera contributed to the protection against GAS bacteria. In these absorption experiments, when antibodies specific to N-acetylglucosamine (i.e., part of the polysaccharide of formula I) were 'removed' from the human sera, the protection from GAS bacteria as determined by opsonophagocytosis assays was lost. As further proof, when the 'removed' or absorbed antibodies to NAG were added back to the absorbed human sera, the reconstituted sera were then capable of bacterial killing. Thus, Example 1 teaches that antibodies specific to GAS polysaccharides are protective against GAS bacteria, and as such, the specification states in Example 7: "The question of whether these carbohydrate antibodies promote opsonophagocytosis of group A Streptococci has been answered affirmatively and the degree of opsonization correlated well the level of anti-carbohydrate antibodies." (page 27, lines 24-28).

The claimed invention is able to elicit a protective immune response. If anti-carbohydrate antibodies are able to induce opsonophagocytosis, then this indicates that these antibodies can bind GAS bacteria and direct an Fc-Receptor mediated immune responses by phagocytes (i.e., opsonophagocytosis). Implicit in such a response are preceding immune response events such as antigen processing, presentation and naïve B-cell maturation (class switching, somatic hypermutation, etc...). In other words, the ability of anti-carbohydrate

antibodies elicited by the claimed methods to be bactericidal indicates an end-point of a successful (protective) immune response. However, in an effort to expedite this application to allowance, applicants have amended the claims to encompass a method of eliciting protective antibodies specific to GASP.

The claims are enabled by the specification because: (1) the quantity of experimentation is not undue (standard methods known in the art of vaccine research are used, i.e., ELISA's, opsonophagocytic assays, and rabbit animal models), (2) both ample guidance and working examples are disclosed (examples of ELISA's, opsonophagocytic assays, and relationships between antibody titers and bactericidal protection are shown), (3) the nature of the invention does not exceed the skill of the art, (4) the assays disclosed in the instant application to determine whether protective antibodies are elicited are standard within the art, and enable one to readily determine whether protective antibodies are elicited; and (5) the breadth of the claims is reasonable, as a method of eliciting protective antibodies specific to GASP is fully supported by the specification (see below).

The instant specification teaches that antibodies specific to GASP are protective (Example 1), and as the specification teaches that GASP vaccines elicit the production of antibodies specific to GASP in a mammal (Example 7), it reasonably follows for one skilled in the art that the specification also supports a method eliciting antibodies specific to GASP which are protective against GAS bacteria.

The Examiner contends the claimed method is non-enabled because according to the Examiner, Example 7 did not explicitly show that the antibodies elicited in rabbits by the GASP vaccine can be protective against infection:

> [T]here is no showing within the instant specification, as originally filed, that the GASP-specific antibodies elicited by the 10 Kd GASP-tetanus toxoid conjugate of Example 7 are 'protective' 'against infection by group A streptococcal bacteria' in a mammal, including a human and a human child. No evidence is of record in the instant specification showing that a conjugate comprising a GASP of formula I having an average size wherein n is a number that falls anywhere in the broad range of 'about 1 to about 50' or 'about 3 to about 30' and wherein GASP is conjugated to a protein (let a lone a protein fragment) elicits a 'protective' immune response against infection by group A streptococcal bacteria in a mammal, a human or a child using a representative number of conjugates of GASP of formula I wherein n falls in the broad size

> range of 'about 1 to about 50' or 'about 3 to about 30'. (page 8, lines 2-13, of official action dated January 11, 2002).

However, as previously argued, the specification teaches antibodies specific to GASP possess a protective ability:

> The question of whether these carbohydrate antibodies promote opsonophagocytosis of group A Streptococci has been answered affirmatively and the degree of opsonization correlated well with the level of anti-carbohydrate antibodies...The importance of the role of the N-acetylglucosamine reactive antibodies in opsonization was attested to by the fact that the absorption of these antibodies from human sera completely abolished the bactericidal activity of the sera and that, when these antibodies were eluted and added back to the bactericidal assays, killing was restored. (page 27, line 24, to page 28, line 4; for the specific experiments, see Example 1)

Therefore, the specification discloses a credible and enabling basis of data from which a method of eliciting protective antibodies specific to GASP in a mammal may be claimed.

Furthermore, the Examiner contends that the specification does not enable a method of eliciting a protective immune response in humans or children. The Examiner has stated: "There is no data within the instant specification showing that an isolated group A streptococcal polysaccharide of any particular size or molecular weight on conjugation to a protein...does elicit a 'protective' immune response in any mammal, especially a human or human child, 'against infection by group A streptococcal bacteria." Applicants respectfully disagree. As argued above, the specification provides data which shows that the claimed conjugates are capable of eliciting antibodies specific to GASP (Example 7), and that antibodies that are specific to GASP can mediate opsonophagocytosis in human sera (Example 1). Moreover, having shown the opsonic activity of the anti-GASP antibodies, and having shown the elicitation of these antibodies in a T-cell dependent manner in a mammal, applicants respectfully assert that the Examiner has provided no basis to support her contention that the instant methods would not work as claimed.

The applicants disagree with the Examiner's ground of rejection because the activity data disclosed in the specification is reasonably correlated with and supports the claimed methods. A reasonable correlation between *in vitro* activity and *in vivo* activity for patentability is a standard different from a standard required by the Food and Drug Administration, which requires proof of efficacy. In a case about a prosthetic device, the Federal Circuit has recently

reminded the Patent Office of the distinction between the FDA and the PTO: "Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." Scott v. Finney, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). The instant specification shows that antibodies specific to GASP are produced in humans that have been infected with GAS bacteria; antibodies specific to GASP are opsonic, bactericidal and therefore protective; and the claimed conjugates can elicit the production of antibodies specific to GASP.

In sum, applicants have amended generic claim 80 to recite: "A method of eliciting protective antibodies specific to group A streptococcal polysaccharide in a mammal..." Example 7 (Table 4) shows that antibodies specific to GASP can be elicited in a mammal by a conjugate claimed in the invention. Example 7 also teaches immunization procedures and an ELISA protocol to determine whether antibodies specific to GASP are indeed elicited. Example 6 teaches how to make claimed conjugates. Example 1 shows that antibodies specific to GASP are bactericidal, and thus protective. Example 1 further discloses explicit guidance for one skilled in the art to determine whether antibodies specific to GASP are protective. Examples 2 and 3 provide further support of the relationship between GAS bacterial infection and its elicitation of antibodies specific to GASP. Accordingly, the claimed invention is enabled by the specification, and does not require undue experimentation for practice. Applicants respectfully request reconsideration and withdrawal of this rejection.

Response to 'New Matter' Rejection under 35 U.S.C. §112, First Paragraph

Claims 80-93 were rejected under 35 U.S.C. §112, First Paragraph, as containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention. In particular, the Examiner contends the recitation of a method which elicits a protective immune response is not supported. Although applicants respectfully disagree as argued previously, applicants have amended the claims to recite a method which elicits "protective antibodies specific to group A streptococcal polysaccharide". Applicants respectfully request reconsideration and withdrawal of this rejection.

Response to Double Patenting Rejection

Claims 61-72 were rejected under the judicially created doctrine of obviousness-type double patenting for being unpatentable over claims 26-33 of U.S. Patent No. 5,866,135. Applicants respectfully disagree with this ground of rejection.

However, Applicants agree to file a terminal disclaimer upon allowance of claims in this application. The filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870 (Fed. Cir. 1991).

AUTHORIZATION

No additional fee is believed due for filing this paper. However, should any additional fee be required, the Commissioner is hereby authorized to charge any fee or credit any overpayment to Deposit Account No. 13-4500, Order No. 2016-4005US1.

In addition, the Commissioner is requested to grant a petition for any extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2016-4005US1.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: April 11, 2002

By: _____
Kenneth H. Sonnenfeld
Registration No. 33,285

Mailing Address:

MORGAN & FINNEGAN, L.L.P.
345 Park Avenue
New York, New York 10154
(212) 758-4800
(212) 751-6849 Telecopier

APPENDIX
Version With Markings To Show Changes Made

80. A method of eliciting [a] protective [immune response] antibodies [in a mammal against infection by] specific to group A streptococcal [bacteria] polysaccharide in a mammal comprising administering a polysaccharide-protein conjugate or polysaccharide-protein fragment conjugate wherein the polysaccharide component of said conjugates is of formula (I)

$$[\rightarrow 2)\text{-}\alpha\text{-L-Rhap-}(1\rightarrow 3)\text{-}\alpha\text{-L-Rhap-}(1\rightarrow]_n\text{-R}$$

3
↑
1
ß-D-GlcpNAc(I)

wherein R is a terminal reducing L-rhamnose or D-GlcpNAc and n is a number from 3 to 50, [sufficient to confer an average molecular weight of the polysaccharide large enough to be protective when said polysaccharide is conjugated to protein or protein fragment,] and wherein [the] said polysaccharide component is covalently [linked] bound to the protein component or protein fragment component[, and wherein the conjugate is administered in an amount effective to elicit a protective response in the mammal against group A streptococcal infection] of said conjugates.

81. The method of eliciting [a]protective antibodies [immune response] specific to group A streptococcal polysaccharide according to claim 80, wherein the mammal is a human.

83. The method of eliciting [a]protective antibodies [immune response] specific to group A streptococcal polysaccharide according to claim [81] 80, wherein n is [about 1 to about 50] 3 to 30.

84. The method of eliciting [a]protective antibodies [immune response] specific to group A streptococcal polysaccharide according to claim 81, wherein the polysaccharide component has a molecular weight of about 10 Kd.

85. The method of eliciting [a]protective antibodies [immune response] specific to group A streptococcal polysaccharide according to claim 81, wherein the protein component is [linked]bound to the polysaccharide component through a secondary amine bond.

86. The method of eliciting [a]protective antibodies [immune response] specific to group A streptococcal polysaccharide according to claim 85, wherein the protein component is any native or recombinant bacterial protein.

87. The method of eliciting [a]protective antibodies [immune response] specific to group A streptococcal polysaccharide according to claim 86, wherein the protein component is selected from the group consisting of tetanus toxoid, cholera toxin, diphtheria toxoid, and CRM_{197}.

88. The method of eliciting [a]protective antibodies [immune response] specific to group A streptococcal polysaccharide according to claim 87, wherein the protein component [of the polysaccharide-protein conjugate] is tetanus toxoid.

89. The method of eliciting [a]protective antibodies [immune response] specific to group A streptococcal polysaccharide according to claim 81, wherein the [polysaccharide] conjugates [is] are administered with a carrier selected from the group consisting of saline, Ringer's solution and phosphate buffered saline.

90. The method of eliciting [a]protective antibodies [immune response] specific to group A streptococcal polysaccharide according to claim 81, wherein the [polysaccharide] conjugates [is] are administered with an adjuvant.

91. The method of eliciting [a]protective antibodies [immune response] specific to group A streptococcal polysaccharide according to claim 90, wherein the

adjuvant is selected from the group consisting of aluminum hydroxide, aluminum phosphate, monophosphoryl lipid A, QS21 and stearyl tyrosine.

92. The method of eliciting [a]protective antibodies [immune response] specific to group A streptococcal polysaccharide according to claim 81, wherein the human is a child.

93. The method of eliciting [a]protective antibodies [immune response] specific to group A streptococcal polysaccharide according to claim 81, wherein the [group A polysaccharide] conjugates [is] are administered in a dosage amount of about 0.1 μg to about 10 μg per kilogram of body weight.

Response to Double Patenting Rejection

Claims 61-72 were rejected under the judicially created doctrine of obviousness-type double patenting for being unpatentable over claims 26-33 of U.S. Patent No. 5,866,135. Applicants respectfully disagree with this ground of rejection.

However, Applicants agree to file a terminal disclaimer upon allowance of claims in this application. The filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870 (Fed. Cir. 1991).

AUTHORIZATION

No additional fee is believed due for filing this paper. However, should any additional fee be required, the Commissioner is hereby authorized to charge any fee or credit any overpayment to Deposit Account No. 13-4500, Order No. 2016-4005US1.

In addition, the Commissioner is requested to grant a petition for any extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2016-4005US1.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: April 11, 2002

By: _____
Kenneth H. Sonnenfeld
Registration No. 33,285

Mailing Address:

MORGAN & FINNEGAN, L.L.P.
345 Park Avenue
New York, New York 10154
(212) 758-4800
(212) 751-6849 Telecopier